WEST Search History

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DATE: Friday, May 28, 2004

Hide?	Set Name	Query	Hit Count
		DB=EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ	
☐	L8	L5 and phosphatase	6
☐	L7	L6 and phosphatase	0
☐	L6	19990303	127
☐	L5	(drug resistance) and (reduc$5|decreas$5|diminish$4)	299
		DB=PGPB,USPT; PLUR=YES; OP=ADJ	
☐	L4	L3 same (phosphatase with inhib$5)	7
☐	L3	(drug resistance) with (reduc$5|decreas$5|diminish$4)	717
		DB=PGPB; PLUR=YES; OP=ADJ	
☐	L2	L1 and drug resistance	1
☐	L1	20020173031.did.	1

END OF SEARCH HISTORY

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* * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

LE 'HOME' ENTERED AT 09:27:11 ON 28 MAY 2004

 file reg
ST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                         ENTRY    SESSION
LL ESTIMATED COST                                         0.21       0.21

LE 'REGISTRY' ENTERED AT 09:27:19 ON 28 MAY 2004

 ....Testing the current file.... screen

TER SCREEN EXPRESSION OR (END):end

 screen 1993 AND 2021 AND 1840 AND 2040

    SCREEN CREATED

 que  AND L1

SSING TERM BEFORE 'AND'
arch expressions cannot begin with operators.

 ....Testing the current file.... screen

TER SCREEN EXPRESSION OR (END):end

 screen 1993 AND 2021 AND 1840 AND 2040

    SCREEN CREATED

loading C:\Program Files\Stnexp\Queries\formlua1.str

      STRUCTURE UPLOADED

 que L3 AND L2

   QUE L3 AND L2

 s l4
MPLE SEARCH INITIATED 09:29:50 FILE 'REGISTRY'
MPLE SCREEN SEARCH COMPLETED -      0 TO ITERATE

0.0% PROCESSED       0 ITERATIONS                                 0 ANSWERS
ARCH TIME: 00.00.01

LL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                      BATCH   **COMPLETE**
OJECTED ITERATIONS:            0 TO        0
OJECTED ANSWERS:               0 TO        0

            0 SEA SSS SAM L3 AND L2

 s l4 ful
LL SEARCH INITIATED 09:29:59 FILE 'REGISTRY'
LL SCREEN SEARCH COMPLETED -     23 TO ITERATE

00.0% PROCESSED      23 ITERATIONS                                 0 ANSWERS
LARCH TIME: 00.00.01

            0 SEA SSS FUL L3 AND L2

 log y
OST IN U.S. DOLLARS                                   SINCE FILE      TOTAL
                                                         ENTRY    SESSION
ULL ESTIMATED COST                                      157.10     157.31

TN INTERNATIONAL LOGOFF AT 09:30:13 ON 28 MAY 2004
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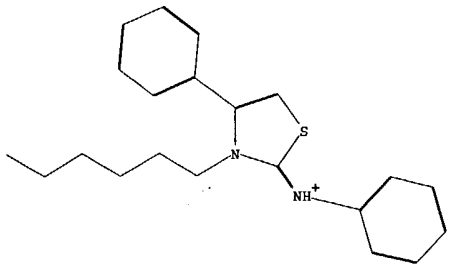

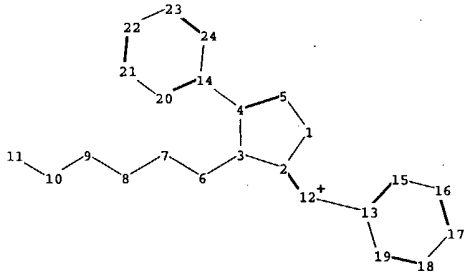

ain nodes :
6 7 8 9 10 11 12
ng nodes :
1 2 3 4 5 13 14 15 16 17 18 19 20 21 22 23 24
ain bonds :
2-12 3-6 4-14 6-7 7-8 8-9 9-10 10-11 12-13
ng bonds :
1-2 1-5 2-3 3-4 4-5 13-15 13-19 14-20 14-24 15-16 16-17 17-18 18-19 20-21
21-22 22-23 23-24
act/norm bonds :
2-3 2-12 3-4 3-6 12-13
act bonds :
1-2 1-5 4-5 4-14 6-7 7-8 8-9 9-10 10-11
rmalized bonds :
13-15 13-19 14-20 14-24 15-16 16-17 17-18 18-19 20-21 21-22 22-23 23-24
olated ring systems :
containing 1 : 13 : 14 :

tch level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS
11:CLASS 12:CLASS 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:Atom
21:Atom 22:Atom 23:Atom 24:Atom

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FILE 'HOME' ENTERED AT 14:11:02 ON 28 MAY 2004

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS,
       BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT,
       CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DISSABS, DDFB, DDFU,
       DGENE, DRUGB, DRUGMONOG2, ...' ENTERED AT 14:11:17 ON 28 MAY 2004

70 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s ((drug resistance)(L)(reduc##### or decreas##### or diminish####)) and
(phosphatase(L)inhib?)
          8   FILE ADISCTI
          7   FILE BIOSIS
          5   FILE BIOTECHABS
          5   FILE BIOTECHDS
          3   FILE BIOTECHNO
  12 FILES SEARCHED...
          4   FILE CANCERLIT
         11   FILE CAPLUS
          3   FILE DISSABS
          1   FILE DDFU
  24 FILES SEARCHED...
          7   FILE DRUGU
  29 FILES SEARCHED...
          7   FILE EMBASE
          6   FILE ESBIOBASE
          1   FILE FEDRIP
  38 FILES SEARCHED...
         24   FILE GENBANK
          6   FILE IFIPAT
          3   FILE LIFESCI
          6   FILE MEDLINE
          1   FILE NTIS
          4   FILE PASCAL
  52 FILES SEARCHED...
          3   FILE PROMT
          7   FILE SCISEARCH
         11   FILE TOXCENTER
       3355   FILE USPATFULL
        155   FILE USPAT2
  66 FILES SEARCHED...
          7   FILE WPIDS
          7   FILE WPINDEX

  26 FILES HAVE ONE OR MORE ANSWERS,   70 FILES SEARCHED IN STNINDEX

L1   QUE ((DRUG RESISTANCE)(L)(REDUC##### OR DECREAS##### OR DIMINISH####)) AND
       (PHOSPHATASE(L) INHIB?)

=> s l1 and PY<2000
          8   FILE ADISCTI
          0*  FILE ADISINSIGHT
   6 FILES SEARCHED...
          2   FILE BIOSIS
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  10 FILES SEARCHED...
        1   FILE BIOTECHNO
  13 FILES SEARCHED...
        3   FILE CANCERLIT
        6   FILE CAPLUS
  18 FILES SEARCHED...
        0*  FILE CONFSCI
        2   FILE DISSABS
  25 FILES SEARCHED...
        3   FILE DRUGU
        3   FILE EMBASE
  32 FILES SEARCHED...
        2   FILE ESBIOBASE
        0*  FILE FEDRIP
        0*  FILE FOREGE
        2   FILE GENBANK
  43 FILES SEARCHED...
        1   FILE LIFESCI
        0*  FILE MEDICONF
        2   FILE MEDLINE
  48 FILES SEARCHED...
        1   FILE PASCAL
  52 FILES SEARCHED...
        0*  FILE PHAR
        2   FILE PROMT
        0*  FILE PROUSDDR
        3   FILE SCISEARCH
  61 FILES SEARCHED...
        6   FILE TOXCENTER
      669   FILE USPATFULL
        2   FILE USPAT2
  68 FILES SEARCHED...

  18 FILES HAVE ONE OR MORE ANSWERS,   70 FILES SEARCHED IN STNINDEX

L2   QUE L1 AND PY<2000

=> d rank
F1        669   USPATFULL
F2          8   ADISCTI
F3          6   CAPLUS
F4          6   TOXCENTER
F5          3   CANCERLIT
F6          3   DRUGU
F7          3   EMBASE
F8          3   SCISEARCH
F9          2   BIOSIS
F10         2   DISSABS
F11         2   ESBIOBASE
F12         2   GENBANK
F13         2   MEDLINE
F14         2   PROMT
F15         2   USPAT2
F16         1   BIOTECHNO
F17         1   LIFESCI
F18         1   PASCAL


=> file f2-11 f13-14 f16-18
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              11.40      11.61

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=> s l2
   3 FILES SEARCHED...
   6 FILES SEARCHED...
   8 FILES SEARCHED...
  11 FILES SEARCHED...
  13 FILES SEARCHED...
L3          45 L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4            23 DUP REM L3 (22 DUPLICATES REMOVED)
                 ANSWERS '1-8' FROM FILE ADISCTI
                 ANSWERS '9-14' FROM FILE CAPLUS
                 ANSWERS '15-16' FROM FILE CANCERLIT
                 ANSWERS '17-19' FROM FILE DRUGU
                 ANSWERS '20-21' FROM FILE DISSABS
                 ANSWERS '22-23' FROM FILE PROMT
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=> d bib abs 1-23

L4 ANSWER 1 OF 23 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN
AN 1997:42596 ADISCTI
DN 800540601
TI New insights into the pathogenesis and management of steroid-resistant asthma.
AU Spahn J D; Leung D Y M; Szefler S J.
SO Journal of Asthma (Jan 1, 1997), Vol. 34, No. 3, pp. 177-194
DT Citation
RE Obstructive Airways Disease
FS Citation
LA English

L4 ANSWER 2 OF 23 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN
AN 1996:10694 ADISCTI
DN 800473930
TI Increase of bone mineral density and anabolic variables in patients with rheumatoid arthritis resistant to methotrexate after cyclosporin A therapy.
ADIS TITLE: Cyclosporin + methotrexate: therapeutic use. Rheumatoid arthritis.
AU Ferraccioli G; Casatta L; Bartoli E.
CS University of Udine, Udine, Italy.
SO Journal of Rheumatology (Sep 1, 1996), Vol. 23, pp. 1539-1542
DT Study
RE Rheumatic Disease
FS Summary
LA English
WC 469

L4 ANSWER 3 OF 23 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN
AN 1996:6556 ADISCTI
DN 800447599
TI How best to use tacrolimus (FK506) for treatment of steroid- and OKT3-resistant rejection after renal transplantation.
AU Eberhard O K; Kliem V; Oldhafer K; et al.
SO Transplantation (May 15, 1996), Vol. 61, pp. 1345-1349
DT Citation
RE Transplant Rejection
FS Citation
LA English

L4 ANSWER 4 OF 23 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN
AN 1996:18948 ADISCTI
DN 800487874
TI Steroid-resistant asthma: evaluation and management.
AU Nimmagadda S R; Spahn J D; Leung D Y M; et al.
SO Annals of Allergy, Asthma & Immunology (Nov 1, 1996), Vol. 77, pp. 345-355
DT Citation
RE Obstructive Airways Disease
FS Citation
LA English

L4 ANSWER 5 OF 23 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN
AN 1996:12779 ADISCTI
DN 800434372
TI Relevance of multidrug resistance to rheumatoid arthritis: development of a new therapeutic hypothesis.
AU Salmon S E; Dalton W S.
SO Journal of Rheumatology (Mar 1, 1996), Vol. 23 (Suppl. 44), pp. 97-101
DT Citation
RE Rheumatic Disease
FS Citation
LA English

L4 ANSWER 6 OF 23 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN
AN 1996:21006 ADISCTI
DN 800464385
TI Current management of asthma patients with corticosteroid resistance.
AU Busse W W; McGill K; Jarjour N N.
SO American Journal of Respiratory and Critical Care Medicine (Aug 1, 1996), Vol. 154, pp. 70-73
DT Citation
RE Obstructive Airways Disease
FS Citation
LA English

L4 ANSWER 7 OF 23 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN
AN 1995:57985 ADISCTI
DN 800406418
TI P-glycoprotein - a marker of cancer-cell behavior.
AU Pinedo H M; Giaccone G.
SO New England Journal of Medicine (Nov 23, 1995), Vol. 333, pp. 1417-1419
DT Citation
RE Cancer Chemotherapy
FS Citation
LA English

L4 ANSWER 8 OF 23 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN
AN 1995:20665 ADISCTI
DN 800379422
TI Management of steroid-resistant asthma.
AU Landwehr L P; Spahn J D; Szefler S J; et al.
SO Clinical Immunotherapeutics (Aug 1, 1995), Vol. 4, pp. 124-137
DT Citation
RE Obstructive Airways Disease
FS Citation
LA English

L4 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
AN 1999:662447 CAPLUS
DN 131:317445
TI Contribution of mdr1b-type P-glycoprotein to okadaic acid resistance in rat pituitary GH3 cells
AU Ritz, Vera; Marwitz, John; Sieder, Sabine; Ziemann, Christina; Hirsch-Ernst, Karen I.; Quentin, Iris; Steinfelder, Hans Jurgen
CS Institute of Pharmacology and Toxicology, University of Gottingen, Gottingen, D-37075, Germany
SO Naunyn-Schmiedeberg's Archives of Pharmacology (**1999**), 360(2), 116-121
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer-Verlag
DT Journal
LA English
AB Okadaic acid as well as other, structurally different, **inhibitors** of serine/threonine **phosphatases** 1 and 2A induce apoptosis in pituitary GH3 cells. Incubation with stepwise raised concns. of okadaic acid resulted in the isolation of cells that were increasingly less sensitive to the cytotoxic effect of this agent. After about 18 mo cells were selected that survived at 300 nM okadaic acid, which is about 30 times the initially lethal concentration This study revealed that a major pharmacokinetic mechanism underlying cell survival was the development of a P-glycoprotein-mediated multidrug resistance (MDR) phenotype. The increase in mRNA levels of the mdr1b P-glycoprotein isoform correlated with the extent of **drug resistance.** Functional assays revealed that increasing **drug resistance** was paralleled by a **decreased** accumulation of rhodamine 123, a fluorescent dye which is a substrate of mdr1-mediated efflux activity. Resistance could be abolished by structurally different chemosensitizers

of P-glycoprotein function like verapamil and reserpine but not by the leukotriene receptor antagonist MK571 which is a modulator of the multidrug resistance-associated protein (MRP). Okadaic acid resistance included cross-resistance to other cytotoxic agents that are substrates of mdr1-type P-glycoproteins, like doxorubicin and actinomycin D, but not to non-substrates of mdr1, e.g. cytosine arabinoside. Thus, functional as well as biochem. features support the conclusion that okadaic acid is a substrate of the mdr1-mediated efflux activity in rat pituitary GH3 cells. Maintenance of resistance after withdrawal of okadaic acid as well as metaphase spreads of 100 nM okadaic acid-resistant cells suggested a stable MDR genotype without indications for the occurrence of extrachromosomal amplifications, e.g. double minute chromosomes.

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
AN 1999:452389 CAPLUS
DN 131:237604
TI Doxorubicin-resistant LoVo adenocarcinoma cells display resistance to apoptosis induction by some but not all **inhibitors** of ser/thr **phosphatases** 1 and 2A
AU Sieder, S.; Richter, E.; Becker, K.; Heins, R.; Steinfelder, H. J.
CS Institute of Pharmacology and Toxicology, University of Gottingen, Gottingen, D-37075, Germany
SO Toxicology (**1999**), 134(2,3), 109-115
CODEN: TXCYAC; ISSN: 0300-483X
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB LoVo adenocarcinoma cells are fairly sensitive to cytostatic drugs, e.g. doxorubicin, but can develop **drug resistance** by expression of a P-glycoprotein-mediated MDR1 phenotype. LoVo cells respond with apoptosis to nanomolar concns. of okadaic acid and micromolar concns. of cantharidic acid. Interestingly, LoVoDx cells which had become about 10-fold less sensitive to doxorubicin by incubation in increasing concns. of this cytostatic drug were also less sensitive to the toxicity of okadaic acid. Resistance to both agents was lost or significantly **reduced** by incubation in drug-free medium for about 4 mo. On the other hand, LoVoDx cells did not lose responsiveness to the structurally different **phosphatase inhibitor** cantharidic acid but were about twofold more sensitive to the cytotoxic effect of this agent. Thus, MDR expression protects LoVo cells from the toxicity of **phosphatase inhibitors** that presumably are substrates of the P-glycoprotein, e.g. okadaic acid and its derivs. but not cantharidic acid, despite the fact that both agents are potent inducers of apoptotic cell death via ser/thr **phosphatase inhibition.**

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
AN 1992:462438 CAPLUS
DN 117:62438
TI The effect of sodium butyrate, interferon-α and verapamil on the sensitivity of ovarian carcinoma cells to adriamycin
AU Manor, Y.; Shneyour, Y.; Nordenberg, J.; Levavi, H.; Ovadia, J.; Novogrodsky, A.; Wasserman, L.
CS Obstet. Gynecol. Dep., Basil Gerald Felsenstein Med. Res. Cent., Petah Tikva, 49100, Israel
SO Cancer Journal (**1992**), 5(2), 101-6
CODEN: CANJEI; ISSN: 0765-7846
DT Journal
LA English
AB Acquired **drug resistance** and drug toxicity are the main limitations to successful chemotherapy. The addition of modifiers is intended to increase drug sensitivity and to **decrease** systemic

toxicity. Modulation of the sensitivity of ovarian tumor cells to adriamycin by sodium butyrate, interferon-α and verapamil was investigated. First passage cultures of cells derived from the ascitic fluid of a clin. refractory ovarian carcinoma patient (BH) and an established ovarian tumor cell line (CAOV-3) were used. Chromosomal G-banding, lipid content and alkaline **phosphatase** activity were investigated. CA 125 and P-glycoprotein were shown by immunoperoxidase staining. P-glycoprotein function was demonstrated using rhodamine. Drug sensitivity was determined by the MTT method. Double minute chromosomes and a homogeneously staining region were found in Bh cells. CAOV-3 and BH were CA 125-pos. Most of BH and several CAOV-3 cells were P-glycoprotein-pos. The P-glycoprotein-transport system was active in BH and less so in CAOV-3 cells. Sodium butyrate increased lipid accumulation whereas interferon-α **decreased** alkaline **phosphatase** activity in CAOV-3 (50%). CAOV-3 were initially more sensitive to adriamycin than BH. Sodium butyrate potentiated the antiproliferative effect of low concns. of adriamycin in Bh while in CAOV-3 the effect was less pronounced. BH and CAOV-3 cells showed different sensitivity profiles to interferon-α. Addition of interferon to adriamycin resulted in an additive growth **inhibiting** effect in BH cells only. Verapamil, known to reverse multidrug resistance, potentiated the antiproliferative activity of adriamycin in BH, whereas in CAOV-3 its effect seemed additive.

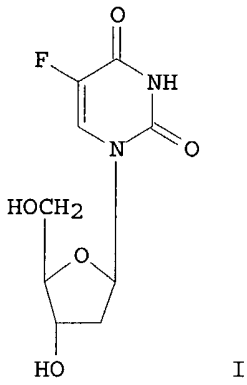
L4 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:307409 CAPLUS
DN 126:338490
TI Concomitant decrease of resistance and modifications of the cytoskeleton after all-trans retinoic acid and phorbol ester treatments in a navelbine-resistant bladder carcinoma cell line
AU Debal, Vincent; Breillout, Fabienne; Manfait, Michel
CS Laboratoire de Spectroscopie Biomoleculaire, GIBSA, IFR 53, U.F.R. de Pharmacie, Reims, 51096, Fr.
SO Anticancer Research (**1997**), 17(2A), 1147-1154
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
AB The bladder carcinoma cell line J82-NVB was selected for resistance to the new vinca alkaloid navelbine. These cells possessed a non-MDR phenotype and were cross-resistant to vinca alkaloids and taxoids. Some morphol. differences between sensitive (J82) and resistant (J82-NVB) cells were observed J82 cells had a heterogeneous population morphol. with both epithelial and spindle shaped cells, while J82-NVB cells were almost all of the epithelial type. Vimentin intermediate filaments were less organized in J82-NVB than in J82 cells. Moreover, desmosomes were present in the membranes of J82-NVB cells but not in J82 cells. These findings suggest that J82 cells are poorly differentiated epithelial cells while J82-NVB cells possess some characteristics of a more differentiated epithelial cell line. After a two-week treatment with all-trans retinoic acid, all the cells became spindle shaped, vimentin filaments reappeared in the cytoplasm of J82-NVB cells and desmosomes disappeared from the membranes of these cells. These changes were accompanied by a decrease from 17 to 4.6 of the resistance factor of J82-NVB cells to navelbine. This decrease in resistance was concomitant with modifications of microtubules assembly regulation mechanisms. After navelbine treatment, microtubule reassembly occurred in resistant but not in sensitive nor in retinoic acid treated cells. Okadaic acid, a protein **phosphatase inhibitor**, **inhibited** microtubule reassembly in resistant cells, and 2-aminopurine, a protein kinase **inhibitor**, induced microtubule reassembly in sensitive cells after navelbine treatment. These findings show that microtubule reassembly after depolymn. is regulated by the kinase/**phosphatase** systems. A treatment with phorbol myristate acetate (PMA), a protein kinase C (PKC) agonist, induced the same morphol. modifications and resistance decrease as retinoic acid

treatment. A specific PKC **inhibitor** (Bisindolylmaleimide) prevented these PMA-induced morphol. modifications and resistance decrease in J82-NVB cells, showing that these effects were mediated by PKC. This study suggests that, in part by acting on some properties of the cytoskeleton, the differentiation modulator, retinoic acid, and the signal transduction modulator, phorbol myristate acetate, can decrease the resistance of J82-NVB cells to microtubule poisons.
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:469305 CAPLUS
DN 119:69305
TI Defective translocation of protein kinase C in multidrug-resistant HL-60 cells confers a reversible loss of phorbol ester-induced monocytic differentiation
AU Slapak, Christopher A.; Kharbanda, Surender; Saleem, Ahamed; Kufe, Donald W.
CS Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA
SO Journal of Biological Chemistry (**1993**), 268(17), 12267-73
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Previous studies have demonstrated that human HL-60 myeloid leukemia cells differentiate in response to phorbol esters. This event is associated with induction of the c-jun early response gene and appearance of a monocytic phenotype. The present studies have examined the effects of vincristine-selected, multi-**drug resistance** on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced HL-60 cell differentiation. The results demonstrate that multi-drug-resistant HL-60 cells, designated HL-60/zinc, fail to respond to TPA with an increase in c-jun transcripts or other phenotypic characteristics of monocytic differentiation. By contrast, treatment of HL-60/zinc cells with okadaic acid, an **inhibitor** of serine/threonine protein **phosphatases**, increase c-jun transcription, growth arrest, and expression of the c-fms gene. Studies were also performed with an HL-60/zinc revertant (HL-60/zinc/R) line that has regained partial sensitivity to vincristine. The finding that HL-60/zinc/R cells respond to TPA with induction of a monocytic phenotype, but not c-jun expression, suggests that c-jun induction is not obligatory for monocytic differentiation. Other studies further demonstrate that the jun-B and fra-1 genes are induced by TPA in both HL-60/zinc and HL-60/zinc/R cells, whereas c-fos expression is attenuated in the HL-60/zinc line. Since TPA activates protein kinase C (PKC), the authors examined translocation of PKC from the cytosol to the membrane fraction. Although HL-60 and HL-60/zinc/R cells demonstrated translocation of PKC activity, this subcellular redistribution was undetectable in HL-60/zinc cells. Activity of the mitogen-activated protein kinase family with associated phosphorylation of c-Jun Y-peptide was markedly **diminished** in TPA-treated HL-60/zinc cells, but not in response to okadaic acid. Taken together, these findings suggest that vincristine resistance confers insensitivity to TPA-induced differentiation and can include defects in PKC-mediated signaling events and induction of jun/fos early response gene expression.

L4 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1985:89764 CAPLUS
DN 102:89764
TI Resistance of CCRF-CEM cloned sublines to 5-fluorodeoxyuridine associated with enhanced phosphatase activities
AU Fernandes, Daniel J.; Cranford, Stephen K.
CS Bowman Gray Sch. Med., Wake Forest Univ., Winston-Salem, NC, 27103, USA
SO Biochemical Pharmacology (**1985**), 34(1), 125-32
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal

LA English
GI



I

AB Resistance of human CCRF-CEM leukemic cells in tissue culture to 5-fluoro-2'-deoxyuridine (FdUrd)(I) [50-91-9] was examined following a single drug exposure (FS sublines). In two FS sublines generated by soft agar cloning of FdUrd sensitive cells in the presence of 1 nM FdUrd, the level of **drug resistance** was maintained at 22- to 30-fold following 1 mo growth in the absence of FdUrd. Characteristic of the FS sublines was a **decreased** accumulation and retention of free intracellular 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP) [134-46-3] averaging 3% of FdUrd sensitive cells, a more rapid rate of disappearance of free FdUMP and FdUMP-bound thymidylate synthase (EC 2.1.1.45) (5,10-methylenetetrahydrofolate:dUMP C-methyltransferase) [9031-61-2], and enhanced alkaline [9001-78-9] and acid phosphatase [9001-77-8] activities. There was no significant difference in the number of nucleoside transport sites per cell among the FS sublines and FdUrd-sensitive cells, indicating that the **decreased** accumulation of FdUMP in the resistant sublines was not the result of impaired FdUrd transport across the plasma membrane. The more rapid turnover of FdUMP-bound thymidylate synthase observed in the FS sublines was neither accompanied by a **decreased** stability of the thymidylate synthase-FdUMP-5,10-methylenetetrahydrofolate ternary complex, nor an enhanced rate of degradation of FdUrd to the less potent agent, 5-fluorouracil [51-21-8]. In addition, the growth rates of the 2 FS sublines were similar to that of FdUrd sensitive cells in medium containing hypoxanthine, methotrexate, and thymidine, indicating that there was no depletion of thymidine kinase (EC 2.7.1.21) (ATP:thymidine-5'-phosphotransferase) [9002-06-6] in the FS sublines. Apparently enhanced activities of acid and alkaline phosphatases, which influence the intracellular accumulation and retention of FdUMP, are important determinants of stable FdUrd resistance in CCRF-CEM cells.

L4 ANSWER 15 OF 23 CANCERLIT on STN
AN 1998641116 CANCERLIT
DN 98641116
TI Phosphorylation of Mdr-1 and prevention of CDC 2 activation correlated with decreased apoptosis induced by paclitaxel in the presence of GL331 (Meeting abstract).
AU Shu C H; Huang T S; Whang-Peng J; Yang W K
CS Veterans General Hospital-Taipei, Taipei, Taiwan 112.
SO Proc Annu Meet Am Assoc Cancer Res, **(1997)** 38 A4116.
ISSN: 0197-016X.
DT (MEETING ABSTRACTS)
LA English
FS Institute for Cell and Developmental Biology
EM 199803

ED Entered STN: 19980417
Last Updated on STN: 19980417
AB Paclitaxel is a microtubule stabilizer and has been used as a promising chemotherapeutic agent for various human cancers, especially advanced ovarian and breast cancers. GL331 is a new semisynthetic podophyllotoxin compound developed to cope with the multiple **drug resistance** property evolved in cancer cells against its congener etoposide. We have found that both paclitaxel and GL331 can cause abnormal CDC 2 activation and subsequent apoptosis in human nasopharyngeal carcinoma (NPC) cell lines. Further analyses on two regulators of CDC 2, CDK 7 and CDC 25, in NPC cells demonstrated that paclitaxel caused an increase in CDK 7 kinase activity, while GL331 treatment elevated the CDC 25 **phosphatase** activity and caused the dephosphorylation of CDC 2 proteins on tyrosine-15 and threonine-14 residues, suggesting that paclitaxel and GL331 elicited distinct mechanisms leading to apoptosis. We further determined the cytotoxic effect and underlying mechanisms by combining paclitaxel with GL331. Our results reveal that the treatment with paclitaxel plus GL331 was less cytotoxic than the treatment with paclitaxel or GL331 alone. Both the activation of CDC 2 kinase and the induction of apoptosis were dramatically **inhibited** in NPC cells treated with 0.1 uM of paclitaxel and 1 uM of GL331 simultaneously. This antagonism is apparently associated with the phosphorylation of Mdr-1 and **decreased** intracellular level of paclitaxel induced by GL331.

L4 ANSWER 16 OF 23 CANCERLIT on STN
AN 75803184 CANCERLIT
DN 75803184
TI BASIS FOR CLINICAL RESISTANCE TO ANTITUMOR NUCLEOSIDE ANALOGS.
AU Hall T C
CS Univ. South. Cal. Cancer Cent., Los Angeles.
SO Ann N Y Acad Sci, **(1975)** 255 235-243.
ISSN: 0077-8923.
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Hierarchical Classification of Proteins
EM 197604
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB The inability to give a safe dose of a drug that will **inhibit** tumor growth in the human patient is termed clinical **drug resistance.** It reflects the relative drug responsiveness in the same patient of the tumor and of the patient's normal tissue. The clinical tumor resistance is commonly equivalent to clinical host sensitivity and the ratio of these 2 factors, drug effect on tumor and drug toxicity to host, provide a ``therapeutic ratio'' that can be tipped toward clinical resistance by either **decreasing** host resistance or increasing tumor resistance. Resistance is related to the therapeutic aim, to the therapeutic aim, to the host tissues at risk, and to the species involved. There are several types of clinical **drug resistance**, including innate or initial **drug resistance**; acquired, secondary or drug-induced resistance; and collateral resistance-acquired pari passu to a drug. Pharmacological bases for resistance include the lack of intake into the body, plasma protein binding, transmembrane transport, extracellular drug destruction, conversion to nucleosides, conversion to the aglycone, destruction of the nucleotide, and alteration of target enzyme. Resistance related to the following drugs is discussed: 6-mercaptopurine ribonucleoside, 6-methylthiopurine ribonucleoside, b-g-deoxythioguanosine, purine nucleotide **phosphatases**, 5-fluorodeoxyuridine, 5-fluorouridine, 1-b-D-arabinofuranosylcytosine, and 5-azacytidine. Mechanisms for circumventing clinical resistance include: **inhibition** of nucleoside phosphorylases, **inhibition** of cytidine deaminase, **inhibition** of purine nucleotide **phosphatases**, search for collateral sensitivity, use of selective combination, delivery to localized tumor areas, synthesized drug activated by catabolism, metabolic conditioning, metabolic activation, differential

genome activation, and specific sequential sensitivity enhancement. (59 refs)

L4 ANSWER 17 OF 23 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1997-42692 DRUGU P
TI Phosphorylation of Mdr-1 and prevention of CDC 2 activation correlated with decreased apoptosis induced by paclitaxel in the presence of GL-331.
AU Shu C H; Huang T S; Whang Peng J; Yang W K
CS Nat.Health-Res.Inst.Taipei; Univ.Yang-Ming
LO Taipei, Taiwan
SO Proc.Am.Assoc.Cancer Res. (38, 88 Meet., 613, 1997) ISSN: 0197-016X
AV Veterans General Hospital, Taipei, Taiwan.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 1997-42692 DRUGU P
AB Paclitaxel (P) is a microtubule stabilizer and has been used as a promising chemotherapeutic agent for various human cancers, especially advanced ovarian and breast cancers. GL-331 is a new semi-synthetic podophyllotoxin compound developed to cope with the multiple **drug -resistance** property evolved in cancer cells against its congener etoposide. In this, the combination of P and GL-331 was antagonistic in NPC cells. Phosphorylation of Mdr-1 and prevention of CDC 2 activation correlated with **decreased** apoptosis induced by P in the presence of GL-331. (conference abstract).
ABEX Both P and GL-331 can cause abnormal CDC 2 activation and subsequent apoptosis in human nasopharyngeal carcinoma (NPC) cell-lines. Further analyses on 2 regulators of CDC 2, CDK 7 and CDC 25, in NPC cells demonstrated that P caused an increase in CDK 7 kinase activity, while GL-331 treatment elevated the CDC 25 **phosphatase** activity and caused the dephosphorylation of CDC 2 proteins on tyrosine-15 and threonine-14 residues, suggesting that P and GL-331 elicited distinct mechanisms leading to apoptosis. The Authors further determined the cytotoxic effect and underlying mechanisms by combining P with GL-331. Treatment with P plus GL-331 was less cytotoxic than treatment with P or GL-331 alone. Both the activation of CDC 2 kinase and the induction of apoptosis were dramatically **inhibited** in NPC cells treated with 0.1 uM of P and 1 uM of GL-331 simultaneously. This antagonism is apparently associated with the phosphorylation of Mdr-1 and **decreased** intracellular level of P induced by GL-331. (PH)

L4 ANSWER 18 OF 23 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1991-26431 DRUGU B P
TI Secretion of Lysosomal Enzymes by Drug-Sensitive and Multiple Drug-Resistant Cells.
AU Warren L; Jardillier J C; Ordentlich P
LO Philadelphia, Pennsylvania, United States
SO Cancer Res. (51, No. 8, 1996-2001, 1991) 2 Fig. 3 Tab. 41 Ref. CODEN: CNREA8 ISSN: 0008-5472
AV Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania 19104, U.S.A.
LA English
DT Journal
FA AB; LA; CT; MPC
FS Literature
AN 1991-26431 DRUGU B P
AB The multiple drug-resistant human lymphoblastic leukemic cell, CEM/VLB100, had a **reduced** content of lysosomal enzymes and a greater relative rate of secretion of these enzymes, than the drug-sensitive cells CEM. The ability of CEM/VLB100 cells to accumulate (3H)vinblastine (VLB) was also greatly **reduced.** However, these effects were not seen in anthracycline- and vincristine-resistant HL60 cells or in CEM/VM-1 cells. Verapamil (VP; Boehr.Mannheim)

inhibited both the efflux of (3H)VLB and the secretion of lysosomal enzymes in CEM/VLB100 cells. In addition, secretion of N-acetylglucosaminidase (NAGA) and efflux of (3H)VLB by CEM/VLB100 cells was enhanced by NaCl.

ABEX The multiple drug-resistant human lymphoblastic leukemic cell, CEM/VLB100, had a **reduced** content of lysosomal enzymes compared with the drug-sensitive cells CEM. The levels of NAGA and beta-galactosidase were **reduced** by 77.1% and 81.1% in the CEM/VLB100 cells. However, these effects were not seen in anthracycline- and vincristine-resistant HL60 cells or in CEM/VM-1 cells. In addition, the rate of secretion of these enzymes was greater in CEM/VLB100 cells than in CEM cells. The % of the total NAGA and beta-galactosidase secreted over 30 min was 8.8% and 5.7%, respectively, in CEM cells, and 14.4% and 11.1%, respectively, in CEM cells. The amount and rate of release of acid **phosphatase** was low and did not vary between the cell lines. VP **inhibited** both the efflux of (3H)VLB and the secretion of lysosomal enzymes in CEM/VLB100 cells. VP at a concentration of 50 uM increased the accumulation of (3H)VLB by 3.4-fold and **inhibited** the secretion of NAGA by 50%. In addition, secretion of NAGA and efflux of (3H)VLB from CEM/VLB100 cells was enhanced by the addition of NaCl to the sucrose-containing medium. The development of multiple **drug resistance** in CEM cells did not alter the rate of synthesis of protein as a whole or of NAGA specifically. When CEM/VLB100 cells were incubated with (3H)VLB and fractionated on a Percoll gradient, the distribution of (3H)VLB among the various populations was similar to that of NAGA. Loss of enzyme and drug took place from the vesicular populations to varying degrees when cells were induced to secrete. (W114/SL)

L4 ANSWER 19 OF 23 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1984-22335 DRUGU P T
TI Drug Resistance in Cancer.
AU Curt G A; Clendeninn N J; Chabner B A
LO Bethesda, Maryland, United States
SO Cancer Treat.Rep. (68, No.1, 87-99, 1984) 2 Fig. 1 Tab. 150 Ref.
CODEN: CTRRDO
AV Clinical Pharmacology Branch, Division of Cancer Treatment, National Cancer Institute, Bldg 10, Rm 6N119, Bethesda, MD 20205, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 1984-22335 DRUGU P T
AB Cellular mechanisms of resistance to cytotoxic drugs in clinical and experimental cancer are reviewed with particular regard to methotr -exate, cytarabine, 5-azacytidine, 5-fluorouracil, alkylating agents (melphalan, mechlorethamine), cisplatin, 6-thiopurines (6-mercapto -purine, 6-thioguanine), steroids, antitubulin agents (vincristine, vinblastine, demecolcine olchicine), antitumor antibiotics (doxo -rubicin) and other relevant agents (PALA, pentostatin, hydroxyurea), with an additional topic of interest being pleiotropic **drug resistance** and its apparent reversibility by calcium-channel blockers (verapamil, diltiazem, nicardipine,niludipine, nimodipine), calmodulin **inhibitors** (prenylamine, trifluoperazine, chloripramine) and an antihypertensive agent (reserpine).

ABEX Established or putative mechanisms of such resistance include the following (specifically altered system as indicated): defective transport for methotrexate, melphalan, mechlormethamine (carrier mediation), cytarabine (membrane nucleoside binding sites) and doxorubicin (efflux); defective metabolic activation for ara-C (deoxycytidine kinase), 5-azacytidine (uridine-cytidine kinase), 5 -FU (uridine kinase, orotate phosphoribosyl-transferase, uridine phosphorylase), 6-mercaptopurine, 6-thioguanine (HGPRT), methotrexate (polyglutamation) and doxorubicin (P450, flavin **reductase**); increased metabolic inactivation for 6-mercaptopurine, 6 -thioguanine (membrane alkaline **phosphatase**

), ara-C (cytidine deaminase), alkylators (intracellular glutathione, metallothionein), bleomycin (bleomycin hydrolase), cisplatin (intracellular metallothionein) and doxorubicin (intracellular glutathione, degradation), altered DNA repair for alkylators, cisplatin and doxorubicin (damaged base excision, excised segment ligation); gene amplification for cadmium (metallothein gene copy number, g-c-n), PALA (aspartate transcarbamylase g-c-n), methotrexate (DHFR g-c-n), doxorubicin (unstable resistance/double-minute chromosomes as gene product), 5-FU (thymidylate synthetase g-c-n) and pentostatin (adenosine deaminase g-c-n); altered targets for methotrexate (DHFR), vincristine (tubulin), hydroxyurea (ribonucleotide **reductase**), 5-FU (thymidylate synthetase), steroids (steroid receptor) and doxorubicin (membrane lipid affinity); altered nucleotide pools for ara-C (CTP, dCTP); salvage pathways for methotrexate (purines) and 5-FU (thymidine kinase); pleiotropic resistance for doxorubicin, vinca alkaloids and deactinomycin (energy-dependent efflux).

L4 ANSWER 20 OF 23 DISSABS COPYRIGHT (C) 2004 ProQuest Information and Learning Company; All Rights Reserved on STN
AN 1999:57023 DISSABS Order Number: AAI9931135
TI SOLID TUMOR STRESS RESPONSES AND DRUG RESISTANCE: INVOLVEMENT OF NF-KAPPAB ACTIVATION IN SENSITIVITY OF EMT6 CELLS TO THE TOPOISOMERASE II-DIRECTED AGENT TENIPOSIDE
AU LIN, Z PING [PH.D.]; KENNEDY, KATHERINE A. [adviser]
CS THE GEORGE WASHINGTON UNIVERSITY (0075)
SO Dissertation Abstracts International, (**1999**) Vol. 60, No. 5B, p. 2076. Order No.: AAI9931135. 194 pages.
DT Dissertation
FS DAI
LA English
AB Stress conditions associated with solid tumor microenvironments, including hypoxia, low pH, and nutrient deprivation have been long implicated in clinical intrinsic **drug resistance**, and associated with tumor cell resistance to topoisomerase II-directed agents in vitro. The involvement of two stress-induced signaling pathways, termed the unfolded protein response (UPR) and the ER-overload response (EOR), in **drug resistance** to the topoisomerase II-directed agent teniposide was investigated in EMT6 mouse mammary tumor cells.

Chemicals that disrupt ER function and physiological stress conditions cause the induction of glucose-regulated protein 78 kDa (GRP78) through the UPR pathway. Treatment of EMT6 cells with the serine/threonine kinase **inhibitor**, H7, **decreased** the basal level of GRP78 mRNA and **inhibited** the induction of GRP78 mRNA by brefeldin A, tunicamycin, and hypoxia. Treatment with the serine/threonine **phosphatase inhibitor**, okadaic acid, slightly increased both basal and brefeldin A-induced GRP78 mRNA levels, and counteracted the **inhibitory** effect of H7 on GRP78 mRNA expression. These results suggest that the UPR pathway/GRP78 induction involves a H7-sensitive serine/threonine kinase.

Disruption of ER function and exposure to hypoxia have also been shown to activate the nuclear transcription factor-κB (NF-κB) presumably through the EOR pathway. Treatment of EMT6 cells with brefeldin A, okadaic acid, and hypoxia all caused the activation of NF-κB. Transient transfection of EMT6 cells with the dominant-negative mutant of IκBα abolished okadaic acid and hypoxia-induced activation of NF-κB. It suggests that stress-induced NF-κB activation in EMT6 cells is mediated in part through the phosphorylation of serines 32 and 36 on IκBα. Furthermore, treatment with the proteasome **inhibitor**, MG-132, attenuated the activation of NF-κB in EMT6 cells treated with brefeldin A, okadaic acid, and hypoxia.

Using clonogenicity assays, the sensitivity of EMT6 cells to teniposide was determined in the presence of **inhibitors** of either the UPR or the EOR pathway. Blockade of the UPR pathway/GRP78 induction by H7 did not reverse BFA-induced resistance to teniposide. In contrast, **inhibition** of the EOR pathway/NF-κB activation

by MG-132 reversed stress-induced resistance to teniposide. Taken together, these results suggest that stress-induced resistance to teniposide is mediated by the activation of NF-κB rather than by the induction of GRP78.

L4 ANSWER 21 OF 23 DISSABS COPYRIGHT (C) 2004 ProQuest Information and Learning Company; All Rights Reserved on STN
AN 1998:32036 DISSABS Order Number: AAR9824827
TI THE EFFECT OF HYPOXIA ON TWO MAJOR CANCER CELL CHARACTERISTICS: UNCONTROLLED PROLIFERATION AND INVASIVENESS
AU KRTOLICA, ANA [PH.D.]; LUDLOW, JOHN W. [adviser]
CS THE UNIVERSITY OF ROCHESTER (0188)
SO Dissertation Abstracts International, (**1998**) Vol. 59, No. 2B, p. 494. Order No.: AAR9824827. 167 pages.
DT Dissertation
FS DAI
LA English
AB Hypoxia or low oxygen availability is commonly experienced by cancer cells within solid tumors. It may also be encountered by malignant cells during their invasion through extracellular matrix in the early stages of metastasis. Hypoxia increases radiation and **drug resistance** of the tumor cells thus impeding the efficient treatment of cancer. It is clear that a better understanding of the effects of hypoxia on cancer cells and the underlying mechanisms involved in hypoxia-induced cell changes will provide knowledge needed for the rational design of cancer therapies to reverse hypoxia induced tumor cell resistance.

The goal of this study was to investigate the effects of hypoxia on two major characteristics of cancer cells--their proliferative ability and invasive potential. We present evidence that hypoxia does not **inhibit** invasion of four different ovarian carcinoma cell lines through the extracellular matrix as assessed by in vitro invasion assays. In addition, we show by zymography and immunoblotting that the detected proteolytic activity, which is due to matrix metalloproteinase MMP-2, is only partially **inhibited** under hypoxic conditions and is not rate limiting in the invasive process.

While invasiveness does not seem to be significantly affected by hypoxia, we found that a hypoxic environment **inhibits** proliferation of both ovarian carcinoma cell lines and a non-transformed cell line, CV-1P, leading to reversible G$\sb1$ cell cycle arrest. This G$\sb1$ arrest is concomitant with activation of the growth suppressive function of the retinoblastoma protein, pRB. The growth suppressive activity of pRB is controlled by its phosphorylation state which varies as a function of cell cycle phase. During G$\sb1$ the hypophosphorylated, active from predominates, while the hyperphosphorylated, inactive from accumulates during S, G$\sb2$ and M phase. We present evidence that hypoxia-induced pRB dephosphorylation results from synergy between an increase in specific pRB-directed **phosphatase** activity and p27 mediated **inhibition** of CDK2 activity. Concomitant with this induction of **phosphatase** activity and CDK2 **inhibition** is a dramatic increase in p27 protein abundance and a **decrease** in cyclin A and E protein levels. Immunoprecipitation studies revealed a high amount of p27 in association with cyclin-CDK2 complexes during hypoxia, while this association is undetectable under aerobic conditions. These data are consistent with the hypothesis that p27 **inhibition** of active cyclin-CDK2 complexes, in addition to lower amounts of cyclin A and E being available for active complex formation, can together result in the observed **decrease** in CDK2 activity during hypoxia. A model of the molecular mechanisms involved in hypoxia-induced cell cycle arrest is proposed.

L4 ANSWER 22 OF 23 PROMT COPYRIGHT 2004 Gale Group on STN

AN 1998:477403 PROMT
TI Hepatocytes as a source of collagen type XVIII endostatin

SO The Lancet, (**12 Sep 1998**) pp. 879.
ISSN: 0099-5355.
LA English
WC 821
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB Collagen type XVIII (C18) belongs to a novel family of basement membrane collagens.1 The 184 aminoacid proteolytic fragment of the carboxyterminus of C18, endostatin, has been identified as a potent endogenous **inhibitor** of angiogenesis.2,3 The strategy to combat tumour growth and metastasis by **inhibition** of angiogenesis is attractive, since solid tumours depend on a vascular supply by newly formed blood vessels. Since endothelial cells, which are required for this process, are non-neoplastic, blocking their migration and proliferation should not lead to resistance. In mice, recombinant endostatin decreased the size of established primary and secondary tumours, and repetitive application of the peptide prevented recurrence.3
Previous Northern analysis showed almost exclusive expression of C18 RNA in the liver,1 but the cellular source of C18, from which endostatin derives, is unknown. To localise the C18/endostatin expressing cells in vivo, we carried out in-situ hybridisation4 with an RNA probe that encodes endostatin, combined with cell-specific immunostaining for vimentin, cytokeratin, and CD31 by the alkaline **phosphatase**-antialkaline **phosphatase** method, on three normal, four cirrhotic, and three neoplastic human livers. The RNA probe was generated by oligo(dT)-primed reverse transcription of human liver RNA with subsequent amplification by oligodeoxyribonucleotide primers corresponding to nucleotides 1483-1501 (CGA CCC ACA AGC CCA CCC G) and 2083-2062 (TCT CCG GCC ATC TGC ATC CAG G, endostatin-encoding region) of the published sequence.1 The amplicon was cloned into pZErO (Invitrogen, Leek, Netherlands) and its authenticity verified by restriction digests, DNA sequence analysis, and expression of the endostatin protein in Escherichia coli and baculovirus (not shown). Plasmids were linearised with XbaI or EcoRI restriction endonuclease, to generate sulphur- 35-labelled antisense or sense (control) run-off transcripts with T7 or SP6 RNA polymerase (BRL Gibco, Eggenstein, Germany). Transcripts were hybridised under high stringency, followed by RNase A digestion to remove mismatched sequences as described.4 For double labelling, immunohistology was done immediately before prehybridisation.4 Positive and negative controls included hybridisation with procollagen [alpha]1(I) and the sense (non-complimentary) endostatin probe, respectively.

L4 ANSWER 23 OF 23 PROMT

AN 1998:153179 PROMT
TI Ontogen Corporation Announces Issuance of US Patent on New Modulator For Restoring Sensitivity to Multi-Drug Resistant Tumor Cells
SO PR Newswire, (**26 Mar 1998**) pp. 326LATH032.
LA English
WC 533
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB SAN DIEGO, March 26 /PRNewswire/ -- Ontogen Corporation, a drug discovery and development company, announced today that the United States (US) Patent and Trademark Office has issued a patent for the use of imidazoles as modulators that restore the sensitivity of multi-drug resistant cancer cells to chemotherapeutic agents. The patent covers methods of use and methods of manufacture pertaining to these novel pharmaceutical compositions added Dr. Barry E. Toyonaga, Ph.D., Chairman, President, CEO and Founder of Ontogen Corporation.
"By automating the medicinal chemistry process, Ontogen has discovered several new drug entities and is optimizing them for enhanced bioavailability, toxicity profiles and therapeutic efficacy," stated Dr. Toyonaga. "Our philosophy has been to create a strong pharmaceutical patent portfolio which protects bioactive substances and their uses, in addition to the hardware and software that we have patented. Ontogen has

shown measurable progress in moving compounds for our three corporate partners into pre-clinical trials and beyond. Now Ontogen is pursuing its own corporate research in cancer multi- drug resistance."
"This recently issued patent further bolsters Ontogen's intellectual property portfolio with 26 pending applications world-wide and 8 allowed or issued patents," added Frank S. Chow, Esq., Ontogen's Chief Patent Counsel. "Earlier, the company patented its work surrounding the **inhibition** of protein tyrosine **phosphatases** (PTPases) which protects Ontogen's non-phosphorus, non- peptide compound libraries from which several selective **inhibitors** to these enzymes are being evaluated in pre-clinical models."

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